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REVIEW ARTICLE

Nordic consensus on treatment of undescended testes

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Abstract

Aim: To reach consensus among specialists from the Nordic countries on the present state-of-the-art in treatment of undescended testicles.

Methods: A group of specialists in testicular physiology, paediatric surgery/urology, endocrinology, andrology, pathology and anaesthesiology from all the Nordic countries met for two days. Before the meeting, reviews of the literature had been prepared by the participants.

Recommendations: The group came to the following unanimous conclusions: (1) In general, hormonal treatment is not recommended, considering the poor immediate results and the possible long term adverse effects on spermatogenesis. Thus, surgery is to be preferred. (2) Orchiopexy should be done between 6 and 12 months of age, or upon diagnosis, if that occurs later. (3) Orchiopexy before age one year should only be done at centres with both paediatric surgeons/urologists and paediatric anaesthesiologists. (4) If a testis is found to be undescended at any age after 6 months, the patient should be referred for surgery—to paediatric rather than general surgeons/urologists if the boy is less than one year old or if he has bilateral or non-palpable testes, or if he has got relapse of cryptorchidism.

INTRODUCTION

The optimal mode of treatment of undescended testes has been a matter of debate for decades. The problems in reaching consensus in the scientific community largely depends on the very long follow-up needed, from diagnosis and treatment in the neonate or in early childhood until full testicular function in adulthood. Randomized controlled studies are still lacking, comparing different modalities with each other until adulthood. However, over the last few years, thanks to research in the Nordic countries and elsewhere, enough data have been accumulated to allow preliminary conclusions on many of the most controversial issues. Therefore, a group of clinical scientists from the five Nordic countries decided to meet and define the present state of knowledge. This report is the condensed result of this meeting, where full consensus was reached. Five different literature reviews were also prepared, before the meeting. These are published as separate articles in this issue.

The following invited participants were unable to attend, but have read and approved the text: L Dunkel, Department of Paediatrics, Kuopio University Hospital, Kuopio, Finland; NE Skakkebaek, Department of Growth and Reproduction, Rigshospitalet, Copenhagen, Denmark.

The participants in the meeting that was held on August 22–24, 2006, in Sigtuna, Sweden, included experts in the field of testicular physiology, paediatric surgery, paediatric urology, paediatric endocrinology, andrology, pathology and anaesthesiology.

PATHOGENESIS AND FUNCTIONAL CONSEQUENCES OF TESTICULAR MALDESCENT

Normal testicular descent in humans requires the formation of a testis from an indifferent gonad, close to the kidney, at about 7 weeks of gestation. The descent of the testis into the scrotum starts with the transabdominal phase that lasts until week 15. The subsequent inguinoscrotal phase is completed by week 35. Numerous genetic and hormonal factors are involved in the regulation of normal testicular descent, but not all have been shown to be of relevance in the pathogenesis of human maldescent. The transabdominal phase is dependent on insulin-like peptide 3 (INSL3) and its receptor LGR8, whereas the inguinoscrotal phase is highly dependent on normal androgen production and action (reviewed in Ref. 1). In childhood, a secondary ascent of the testis from the scrotum may occur, the aetiology and consequences of which are yet unclear. This secondary

ascent ('aquired cryptorchidism') may explain why the accumulated orchiopexy rates are often higher than prevalence rates of congenital cryptorchidism in the same populations (2–4).

Endocrine and genetic disorders can cause maldescent of the testis, but in the majority of cases no distinct aetiology can be determined. Any disturbance of normal testicular differentiation and function may compromise its normal descent. In unilateral cryptorchidism, the retained testis is most often smaller than its scrotal counterpart already at birth, suggesting prenatal testicular maldevelopment (5). In addition, changes caused by the malposition itself (e.g. increased testicular temperature) can add further damage. The more severe the testicular dysgenesis, the more severe the cryptorchidism. For example, individuals with gonadal dysgenesis frequently present with high intra-abdominal testes. Such patients often present with abnormal karyotype, e.g. 45X/46XY mosaicism.

Mutations/polymorphisms of the gene for INSL3 and its receptor LGR8 seem to be rare causes of cryptorchidism in boys, even in studies of familial cryptorchidism (6).

Insufficient androgen action, e.g. in the case of hypogonadotropic hypogonadism, impaired Leydig cell function or androgen receptor mutations, is often associated with congenital cryptorchidism, as are malformations of the caudal body segment, such as spina bifida. There is also emerging suspicions that life style factors, such as maternal smoking during pregnancy (7) and environmental factors, such as endocrine disrupting chemicals (8,9) may contribute to some cases of undescended testis.

Impairment of spermatogenesis is the major problem in undescended testes. Untreated bilateral cryptorchidism leads to azoospermia, which is possibly ameliorated by treatment. Treated unilateral cryptorchidism is not reported to affect fertility, although also in these patients sperm count is reduced (reviewed by 10,11). There is evidence that the age at orchiopexy matters for semen quality in adulthood, as the loss of germ cells becomes more pronounced the older the child is at surgery (12). In adult men, impaired spermatogenesis is often reflected by high FSH and low inhibin B. It is yet unresolved whether also Leydig cell function is compromised.

Cryptorchidism is associated with a 4–5-fold higher risk of testicular cancer. These observations strongly indicate that in most cases cryptorchidism is caused by a primary testicular maldevelopment that occurred already in utero. However, testicular function deteriorates further if the testis is left in a position above the scrotum.

DIAGNOSIS OF UNDESCENDED TESTIS

The clearest classification system divides undescended testis into non-palpable and palpable testes. However, the latter need a more precise definition. We suggest the following criteria, using the middle of the testis as a reference for each position: (1) Suprascrotal including inguinal and non-palpable testes. (2) Upper portion of the scrotum or (3) Lower portion of the scrotum. If a testis spontaneously assumes a suprascrotal position and cannot be pulled down into the scrotum, it is diagnosed as an undescended testis, which needs treatment. The borderline cases, often called retractile testes, present the most difficult diagnostic dilemma. If the testis is in a suprascrotal position and can be pulled down to the upper scrotum, but does not remain there after exhausting the cremasteric activity, it is also defined as an undescended testis, and needs treatment. If it remains in the upper or lower scrotal position after the traction is released, the current recommendation is that these testes should not be subject to treatment. However, the patient should be followed at least once a year, due to the markedly increased risk of later ascent. Since some retractile testes may show a gradual histological deterioration and a reduction in volume, compared to the contralateral testis, treatment may be considered (13).

In some rare cases, ectopic testes can be femoral or perineal and should be regarded and managed as undescended testes.

In general, the position of the testes may change during childhood. Boys should get repeated examinations of the testicular position during childhood at the stipulated physical examinations done in child health care. Especially the boys with undescended testes at birth, with spontaneous descent during the first months of age, are at high risk of later reascent.

RESULTS AND POSSIBLE SIDE EFFECTS OF TREATMENT

Two principally different approaches to treatment of undescended testes have been used for many years: Surgery (orchiopexy) and hormonal treatment. The results of orchiopexy and the two modes of hormonal treatment (human gonadotropic hormone, hCG, gonadotropin releasing hormone, (hCG) GnRH, LHRH) will be shortly reviewed below.

Surgical treatment

The success rate of operative treatment, defined as a scrotal position of the testis, without atrophy, is related to the type of undescended testis (palpable and non-palpable), the choice of operative procedure and the age at the time of surgery. It is generally accepted that the possible surgical failures such as postoperative testicular atrophy and recurrent cryptorchidism cannot be estimated until follow-up at least one year postoperatively. In the analysis of 64 articles including 8425 undescended testicles, the anatomical success rate, in expert hands, varied between 74% for abdominal and 92% for testes located beyond the external ring (14). In the past decade, the corresponding success of orchiopexy for inguinal testes has been reported to be >95%. For abdominal testes, the reported success for orchiopexy has been >85–90% in most series with single stage orchiopexy or two stage Fowler-Stephens orchiopexy, both with open surgical or laparoscopic technique (15).

However, having a palpable testis in the scrotum does not assure normal function. Normal function would entail normal hormone production and normal spermatogenesis. Generally, adult men with persistent bilateral

cryptorchidism have azoospermia, whereas after operation in childhood about 28% of patients with bilateral cryptorchidism have at least 20 millions sperms/mL of the ejaculate. In unilateral cases the dependency on proper treatment is not that strong, since about 50% of men with persistent unilateral cryptorchidism have at least 20 millions sperms/mL. as compared to about 70% after orchiopexy. Surgery significantly improved sperm count in uni- and bilateral cases, even if most patients in this study underwent orchiopexy after 2 years of age (12).

The impact of orchiopexy on Sertoli cell function may be reflected by postoperative levels of serum inhibin B. In adulthood, higher levels of inhibin B were found in men who underwent orchiopexy before 2 years of age than in men with surgery at higher age (16). Orchiopexy in late childhood appears to be associated to impaired Leydig cell function in adulthood (17,18).

The side-effects of surgery include pain, haematoma, infection, and the risk of anaesthetic complications. Testicular atrophy and damage of the vas deferens may also occur in rare cases, especially when performing surgery a second time (reviewed by Ref. 15).

Hormonal treatment

We found three meta-analyses of randomised trials concerning the effect of hormonal treatment on testicular descent (19–21). Most of the studies using hCG or LHRH show overall efficacy of about 20%, less if retractile testes were excluded. The efficacy depends on the initial position of the testes. The lower the position of the testis, the higher the rate of descent. However, after hormonal treatment, up to 25% of the testes reascend to a suprascrotal position later on (21).

Hormonal treatment following orchiopexy has been proposed to have beneficial effects on sperm count (22,23). These findings need confirmation by other groups before being incorporated into clinical practice.

Reported side effects of hormonal treatment include repeated pain at the injection site, growth of the penis, pubic hair, pain in the groin, erection pain, behavioural problems, temporary inflammatory changes in the testes, germ cell apoptosis and, importantly, reduction in the number of germ cells and the size of the testes in adulthood (24,25). The adverse effects of hormonal treatment may be age-dependent, most harm being caused at 1–3 years of age (26).

PREFERRED METHODS FOR TREATMENT OF UNDESCENDED TESTES

Considering the efficacy and the possible side effects of the different treatment modalities described above, we find surgery to be the primary choice for most patients. The efficacy of hormonal treatment is poor, and several potential side effects after hCG-treatment in childhood have been described, including acute inflammatory changes in the testis and reduced testicular volume in adulthood. Despite these concerns, in rare special cases of undescended testes, hormonal treatment might be considered. We have not found enough evidence for a beneficial effect of hormonal treatment before or after surgery.

RECOMMENDED SURGICAL TREATMENT OF UNDESCENDED TESTES

Palpable undescended testes

Today, the surgical therapy for the palpable undescended testis is orchiopexy with creation of a subdartos pouch. Transverse groin incision should be made over the internal ring. The external oblique aponeurosis is usually incised laterally from the external ring in the direction of its fibers, avoiding injury to the ilioinguinal nerve. Once located, the testis and spermatic cord are freed and notification of testis size, position and abnormalities should be done.

The testis and hernia sac are dissected from the canal. Retroperitoneal dissection through the internal ring may provide additional cord length for the testis to reach the scrotum. A subdartos pouch is created (27).

The Bianchi single high scrotal incision technique for orchiopexy in boys with palpable undescended testes distal to the external inguinal ring is an optional technique for many surgeons. The retroperitoneal dissection is however crucial for the success of both surgical procedures. Bilateral cases can be done in a one-stage procedure.

Unilateral non-palpable undescended testis

When the testis is non-palpable, diagnostic laparoscopy through an umbilical port is useful for determining which surgical approach should be taken. The operative procedure is chosen according to pathoanatomical findings related to the testis and vessels and to the surgeons preferences.

Bilateral non-palpable undescended testes

If both testes are missing and/or ambiguity of the sex assignment of the patient is raised, the patient is referred to the paediatric endocrinology unit immediately after birth for diagnostic work-up.

Later laparoscopy is performed to determine surgical therapy in the same manner as for unilateral, nonpalpable undescended testes. Diagnostic ultrasound investigation has no value for management of the testis. Operation should preferentially be done at one side at a time in order to evaluate the operative result before proceeding to the contralateral side. Thus, in case of postoperative atrophy there is a possibility do minimal surgery on the other side, aiming at bringing the contralateral initially non-operated testis to a palpable position. Although spermatogenesis in this still suprascrotal testis may be compromised, it will hopefully have preserved hormonal production.

Testicular biopsy

Paediatric testicular biopsy during orchiopexy should only be performed in case of ambiguous genitalia, chromosomal disorders or as a part of clinical studies.

OPTIMAL AGE FOR TREATMENT OF UNDESCENDED TESTES

The optimal age for treatment should consider the final (adult) results on both spermatogenesis and hormone production, as well as risk for tumours.

Spermatogenesis

Few studies have assessed semen quality in relation to age at orchiopexy. Due to the variable previous treatment regimens, the age range at treatment is usually higher than in current recommendations. Orchiopexy in bilateral cryptorchidism led to a normal sperm count in 76% of the men if surgery was performed between 10 months and 3 years of age, compared to 26% (9–51%) following surgery between 4 and 14 years of age (28,29). These findings are supported by several animal studies demonstrating that earlier intervention preserves spermatogenesis and fertility. Animal studies cannot be translated directly into human medicine to determine optimal timing of operation, but a recent prospective randomised study shows that orchiopexy at age 9 months results in significantly larger testicular volume at age 4 years compared to orchiopexy at 3 years of age (30). Whether this difference will sustain until adulthood and result in improved spermatogenesis must await longer follow-up.

Testicular endocrine function

Whether or not early orchiopexy influences the altered endocrine function of the testis in adulthood remains unresolved. In bilateral cases the parents should also be advised, that the patient should undergo examination in early adolescence, to ensure normal pubertal masculinisation.

Testicular cancer

It remains to established whether orchiopexy at an early age, e.g. before 2 years of age, will decrease the risk of testicular cancer. The parents should be informed that the boy has an elevated risk of testicular cancer after puberty.

Psychological aspects

To our knowledge there are no specific studies addressing the impact of age of orchiopexy on the psychological outcome of cryptorchid patients. Although studies on the age of surgery of genitals in general suggest that operation should be avoided between 2 and 6 years of age (31), there are to our knowledge no documented psychological sequelae after orchiopexy at any age, provided that the parents and the child have been adequately informed about the procedure, and that general anaesthesia has been used. Furthermore, our recommendation is that surgery for congenital cryptorchidism should be performed before 1 year of age, if possible.

Conclusions regarding age at operation

Thus, there are no hard data on the optimal age of orchiopexy although many recent findings suggest that early intervention (<1 years of age) is most beneficial. Given the high rate of spontaneous descent during the first months of life, surgery of undescended testes diagnosed at birth should probably not be performed before 6 months of age.

FACILITIES AND QUALIFICATIONS NEEDED FOR SURGICAL TREATMENT OF UNDESCENDED TESTES

Ideally, all cases of undescended testes should be operated on by paediatric surgeons or paediatric urologists. However, in most countries and for the time being this is not realistic, but at least three minimal requirements have to be met to ensure patients safety:

1. Operation of congenital cryptorchidism at the recommended age of 6–12 months should be performed by paediatric surgeons or paediatric urologists.
2. All bilateral cases, non-palpable testes and re-do cases, irrespective of age, should also be performed by paediatric surgeons or paediatric urologists.
3. Paediatric anaesthesiologic expertise is required when operation is performed before the age of 1 year.

When the boy is referred at a later age, palpable unilaterally undescended testes may be operated on by general surgeons and urologists with special interest and experience (31,32).

PAEDIATRIC ANAESTHESIA FOR INFANT ORCHIOPEXY

Today the anaesthetic risk, even during infancy, is low (33–35). Patel and Hannalah have also demonstrated that outpatient surgery in infants and children is safe (36). These issues on patient safety are all statements from major centres with specialized paediatric anaesthesia services. The reasoning rests on the notion that the increased complexity in younger children, particularly under the age of 12 months, is more safely handled by an experienced paediatric anaesthesiologist than by an experienced general anaesthesiologist who is relatively inexperienced in paediatric anaesthesia and who usually performs in an environment that is not entirely dedicated to paediatrics.

Some areas of paediatric surgery could be characterized as 'chirurgia minor'. 'Anaesthesia minor' does, however, not exist. The complication rate in infants is first comparable to the one that is found in patients 75 years and older (37). Hence, surgery in infants requires the anaesthetic to be administered at a medical centre with a specialized service for paediatric anaesthesia. Therefore, in the planning of surgery for un-descended testicles at the age of 6–12 months, the current patient safety records require that the anaesthesia must be carried out by specialists. Since this type of surgery is fairly common, proposed changes in guidelines and routines for surgical treatment of un-descended testicles, such as these, also ask for changes in patient flows putting higher quantitative and financial demands on paediatric centres. A compromise with regard to the requirement of specialist treatment is not to be recommended and will have an impact on patient safety.

SUMMARY: SUGGESTED ROUTINES FOR MANAGEMENT OF UNDESCENDED TESTES AT THE PAEDIATRIC UNIT

(See Fig. 1.) After diagnosis of congenital cryptorchidism in a newborn boy, he should be referred to a paediatric

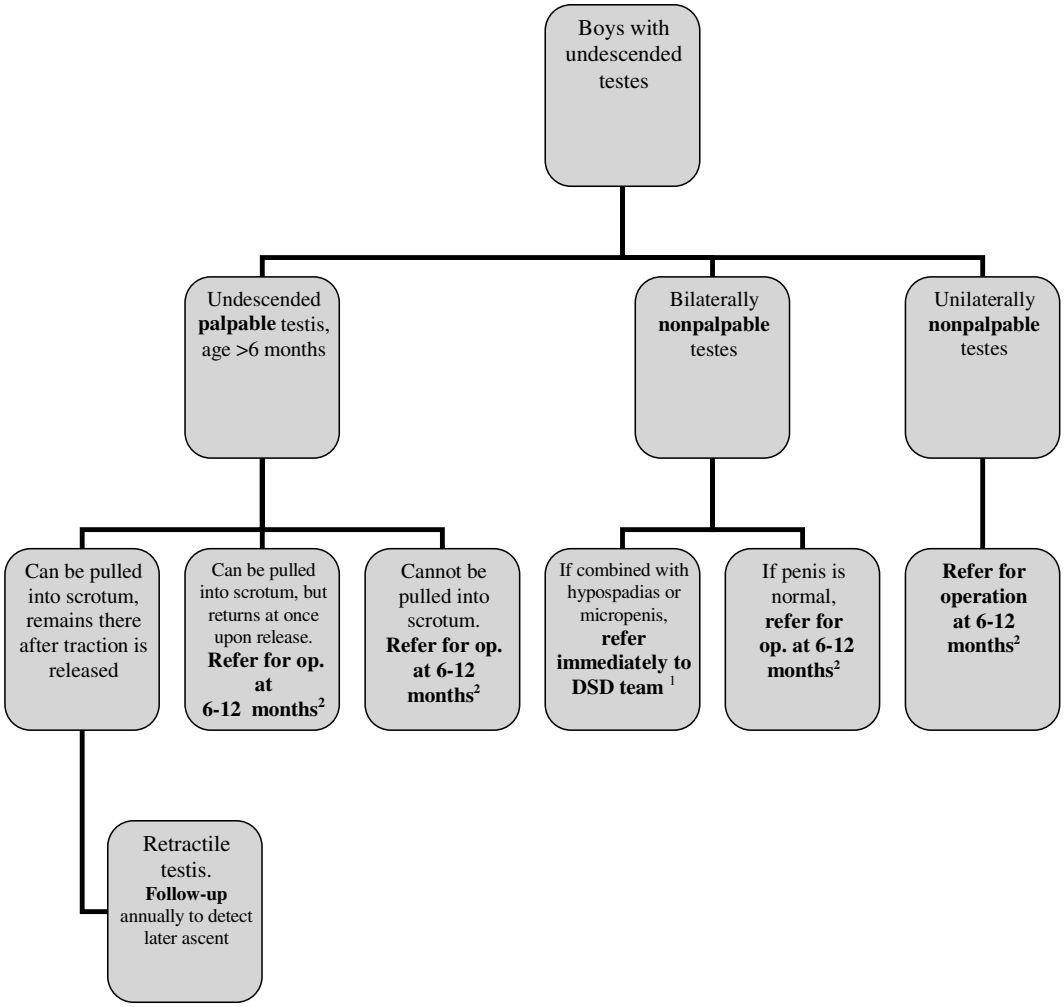

Figure 1 Schematic representation of a decision tree that can be used for management of boys with undescended testes. See also text, for a more detailed discussion.

surgeon/urologist not later than at 6 months of age. If the testis by then has descended into the scrotum, or if it is classified as 'retractile', the parents should be advised that annual follow-up will be needed throughout childhood, since there is a very significant risk for reascent. If the testis is not descended by 6 months of age the paediatric surgeon/urologist schedules orchiopexy before one year of age. If a testis is found to be undescended at any age after 6 months, the patient should be referred for surgery–to paediatric surgeons/urologists if the boy is less than one year old or if he has bilateral or non-palpable testes, or if he has got relapse of cryptorchidism. Unilateral cases >1 year old may also be operated by other competent surgeons.

[1]A DSD team should include experts with experience of management of children born with undetermined sex, including endocrinology, urology, gynaecology, medical genetics and child psychiatry.

[2]Orchiopexy should ideally be made between 6 and 12 months of age. If the testis is found to be undescended at an older age, the boy should be referred as soon as the diagnosis is made.

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